## REMARKS

After entry of the present amendment, claims 25-45 will be pending in the present application. Claims 1-24 as originally filed are canceled herein without prejudice and new claims 25-45 are added. Original claims 1-24 have been replaced with new claims 25-45 in view of the Restriction Requirement, to limit the claims to the elected subject matter, as explained in more detail below. Applicants reserve the right to file one or more divisional applications to prosecute claims directed to the non-elected subject matter, and/or subject matter encompassed by original claims 1-24.

**Support for the New Claims**

The new claims are fully supported by the application as originally filed and no new matter has been added. Support for new claims 25-45 is found throughout the specification, for example, as indicated below.

Claims 25 and 27-30: page 2, paragraph 007; page 3, paragraph 0010; page 4, paragraph 0012; page 5, paragraph 0015; page 8, paragraph 0025; page 37, Table 2; page 42, paragraph 00105; pages 43-45, paragraphs 00106 – 11019.

Claim 26: page 42, lines 8-12; page 43, Table 3.

Claims 31-37: page 43, Table 3.

Claims 38-41: page 12, lines 17-21; page 14, lines 16-17.

Claim 42: page 14, paragraph 0044, lines 6-10; page 14, paragraph 0045, line 16-17.

33. (New) The isolated nucleic acid of claim 26, wherein said thiolation domain comprises an amino acid sequence selected from the group consisting of amino acids 961-1030 of SEQ ID NO: 13; amino acids 991-1059 of SEQ ID NO: 14; amino acids 2054-2122 of SEQ ID NO: 14; amino acids 3123-3191 of SEQ ID NO: 14; amino acids 4161-4228 of SEQ ID NO: 14; amino acids 5193-5260 of SEQ ID NO: 14; amino acids 5755-5824 of SEQ ID NO: 14; amino acids 6805-6873 of SEQ ID NO 14; amino acids 994-1062 of SEQ ID NO: 15; amino acids 2042-2110 of SEQ ID NO: 15; amino acids 3097-3165 of SEQ ID NO: 15; amino acids 4136-4202 of SEQ ID NO: 15; amino acids 5200-5268 of SEQ ID NO: 15; amino acids 6281-6350 of SEQ ID NO: 15; amino acids 7344-7411 of SEQ ID NO: 15 and amino acids 8381-8449 of SEQ ID NO: 15.

34. (New) The isolated nucleic acid of claim 26, wherein said thioesterase domain comprises an amino acid sequence of amino acids 8450-8695 of SEQ ID NO. 15.

35. (New) The isolated nucleic acid of claim 27, wherein said nucleic acid sequence encodes an amino acid sequence selected from the group consisting of : amino acids 1-470 of SEQ ID NO. 13, amino acids 471-959 of SEQ ID NO. 13 and amino acids 961-1030 of SEQ ID NO. 13.

36. (New) The isolated nucleic acid of claim 28, wherein said nucleic acid sequence encodes an amino acid sequence selected from the group consisting of: amino acids 1-517 of SEQ ID NO: 14; amino acids 518-990 of SEQ ID NO: 14; amino acids 991-1059 of SEQ ID NO: 14; amino acids 1106-1560 of SEQ ID NO: 14; amino acids 1561-2052 of SEQ ID NO: 14; amino acids 2054-2122 of SEQ ID NO: 14; amino acids 2159-2618 of SEQ ID NO: 14; amino acids 2619-3122 of SEQ ID NO: 14; amino acids 3123-3191 of SEQ ID NO: 14; amino acids 3237-3697 of SEQ ID NO: 14; amino acids 3698-4160 of SEQ ID NO: 14; amino acids 4161-4228 of SEQ ID NO: 14; amino acids 4241-4718 of SEQ ID NO: 14;

Claims 43-45: page 5, lines 9-12; page 17, paragraph 0057; page 19, paragraph 0062; page 21, paragraph 0069; pages 22-28, paragraphs 0071-0089; Example 3, pages 52-55, paragraphs 00126-00132.

**Amendments to the Specification**

The specification has been amended to correct obvious typographical errors. For example, the serial number of one of the priority applications referred to in the first paragraph of the specification incorrectly appeared as "90/910,813"; this has been corrected to "09/910,813". In addition, the specification in many instances incorrectly referred to the number of ORFs in the present invention as "32", and in one instance, as "34." It is apparent upon review of the Sequence Listing, as well as other portions of the specification (see, e.g., pages 11-13, paragraph 0040), that the correct number of ORFs in the present invention is 33. Accordingly, the specification has been amended to reflect the correct number of ORFs as being "33." References to the corresponding SEQ ID NOS in the specification have been amended as well. In addition, on page 4, line 2, the specification has been amended to replace the expression "or most preferably or more" with "or most preferably five or more" as it is apparent that the word "five" was inadvertently omitted. Support for this amendment may be found in claim 18 as originally filed.

**Response to Restriction Requirement**

In the Office Action mailed on September 26, 2003, the Examiner imposed a restriction requirement in which the Examiner divided the claims 1-24 as originally filed into the following groups:

SuperGroup A: Claims 1-10 and 19-21, drawn to nucleic acids related to sequences encoding any of SEQ ID NOS. 2-34, related vectors and host cells thereof, classified in class 536, subclass 23.1;

SuperGroup B: Claims 11-13, drawn to gene clusters encoding polypeptides that produce ramoplanin and/or analogs thereof, classified in class 536, subclass 23.2;

SuperGroup C: Claims 14-18, drawn to polypeptides related to sequences of any of SEQ ID NOS. 2-34, classified in class 530, subclass 350; and

SuperGroup D: Claims 22-24, drawn to methods of using polypeptides related to sequences of any of SEQ ID NOS. 2-34, classified in class 435, subclass 76.

The Examiner further divided each of the SuperGroups above into the following Groups:

Groups 1-33: drawn to nucleic acids and related products related to SEQ ID NOS. 2-34, respectively (encoded amino acid sequences). The Examiner noted that some of the claims of SuperGroup A would be excluded in some of the noted Groups because some ORFs are excluded in Claims 2, and 6-10.

Group 34, drawn to the gene cluster. Only one Group is in SuperGroup B.

Groups 35-67, drawn to polypeptides related to SEQ ID NOS. 2-34, respectively. The Examiner noted that some of the claims of SuperGroup C would be excluded in some of the noted Groups because some ORFs are excluded in Claim 15.

Groups 68-100, drawn to methods of using polypeptides related to any of SEQ ID NOS. 2-34, respectively. The Examiner noted that some of the claims of SuperGroup D would be excluded in some of the noted Groups because some ORFs are excluded in Claim 24.

The Examiner contends that these groups are distinct, each from the other.

In response, Applicants elect the claims of SuperGroup A, claims 1-10 and 19-21, drawn to nucleic acids related to sequences encoding any of SEQ ID NOS. 2-34, and related vectors and host cells thereof, for prosecution in the instant application. Applicants further provisionally elect, with traverse, the claims drawn to nucleic acids and related products related to SEQ ID NO: 15 (ORF 14) (encoded amino acid sequences) for prosecution in the instant application.

However, Applicants respectfully submit that the claims drawn to nucleic acids and related products and methods relating to SEQ ID NOS: 13, 14, 15 and 18 (ORFs 12, 13, 14 and 17) should be combined and examined together in the present application. Each of these sequences encodes structurall similar non-ribosomal peptide synthases which are involved in the biosynthesis of the cyclic depsipeptide core of the ramoplanin molecule.

The biosynthetic gene cluster of ramoplanin contains 33 open reading frames (ORFs) corresponding to SEQ ID NOS: 2-34. However, only nine (9) of these ORFs (i.e., ORFs 9, 11, 12, 13, 14, 15, 17, 26 and 27) are directly involved in the formation of the ramoplanin depsipeptide core. Of these nine ORFs, only four (i.e., ORFs 12, 13, 14, and 17) encode non-ribosomal peptide synthases which are responsible for the modular biosynthesis of the peptide backbone of ramoplanin. The four non-ribosomal peptide synthases encoded by these ORFs share certain amino acid motifs and are thus structurally related. For example, the amino acid sequences encoded by SEQ ID NOS: 13, 14, 15 and 18 (ORFs 12, 13, 14 and 17) share ten highly conserved core motifs A1-A10 in their adenylation domains (see Figure 3A and accompanying description at pages 8-9, paragraph 0028 of the specification).

Applicants respectfully submit that since the proteins encoded by these ORFs share structural features and have similar functions, that claims directed to SEQ ID NOS: 13, 14, 15, and 18 (ORFs 12, 13, 14, and 17) should be examined together in the instant application. Applicants respectfully submit that these four sequences constitute a reasonable number of sequences to be claimed in a single application pursuant to MPEP 803.04.

Accordingly, Applicants submit herein a new set of claims 25-45 which are limited to SEQ ID NOS: 13, 14, 15 and 18 (ORFs 12, 13, 14, and 17). The new claims recite isolated nucleic acids which encode a domain of a ramoplanin non-ribosomal peptide

synthase, wherein the ramoplanin non-ribosomal peptide synthase is selected from SEQ ID NOS: 13, 14, 15 and 18 (ORFs 12, 13, 14, and 17). The specific domains of these non-ribosomal peptide synthases (i.e., condensation, adenylation, thiolation and thioesterase domains) are recited in dependent claims. In addition, the approximate amino acid ranges of the condensation, adenylation, thiolation and thioesterase domains of these enzymes are further recited in dependent claims. Applicants have also included claims directed to expression vectors and host cells which comprise the claimed nucleic acids, as well as a claim directed to a method of preparing ramoplanin or an analog thereof using the claimed host cells and vectors. Applicants have included this method claim in view of the procedures for rejoinder of claims set forth in MPEP 821.04.

**Corrections to Sequence Listing and Response to the Examiner's Comments**

The Examiner has noted certain errors in the Sequence Listing. In response, Applicants enclose herewith a Substitute Sequence Listing in which the errors have been corrected accompanied by a paper entitled "Transmittal of Substitute Sequence Listing". In addition, Applicants submit herewith an alignment of the full-length, exactly encoding DNA contig sequence (SEQ ID NO: 1) with each of polypeptide sequences of SEQ ID NOS: 2-34 (see Appendix A attached hereto). Applicants wish to thank the Examiner for the useful comments and suggestions regarding the alignment discussed in the telephone conversation between the Examiner and Applicants' representative Anne Coughlin on February 23, 2004.

In the September 26, 2003 Office Action, the Examiner contends that (a) no sequence for ORFs 2 and 3 is noted, and (b) two sequences for ORF 5 (SEQ ID NOs: 4 and 6) are noted. Applicants' representative has carefully reviewed the Applicants' copy of the original Sequence Listing (which is believed to be identical to the one filed), and respectfully submits that the original Sequence Listing does in fact include an amino sequence corresponding to ORF 2 (SEQ ID NO. 3, having 304 amino acid residues, corresponding to nucleotides 3118 – 4032 of SEQ ID NO: 1), and an amino acid sequence corresponding to ORF 3 (SEQ ID NO: 4, having 336 amino acid residues, corresponding to nucleotides 4038 – 5048 of SEQ ID NO. 1). In addition, the original Sequence Listing includes only one sequence for ORF 5 (SEQ ID NO. 6, having 336 amino acid residues, corresponding to nucleotides 7703 – 6693 of SEQ ID NO: 1). Applicants note that while the present Sequence Listing does not include separate sequence identifiers (SEQ ID NOS) for the nucleotide sequences of each of ORFs 2-34, the specification and the Sequence Listing do provide the specific nucleotide ranges within the contiguous sequence of SEQ ID NO: 1 for each of ORFs 2-34. See the specification at page 11, line 32 to page 13, line 17 and pages 1-4 of the Sequence Listing as originally filed.

Applicants note, however, that on page 1 of the original Sequence Listing, the information under numerical identifiers <220> - <223> for ORF 3 (SEQ ID NO. 4, corresponding to nucleotides 4038 – 5048) inadvertently appears twice. This error has been corrected in the Substitute Sequence Listing enclosed herewith.

The Examiner contends that no sequences for ORFs 13 and 14 are noted but points out that SEQ ID NOs: 14 and 15 are each 4999 long and appear to be truncated forms of ORFs 13 and 14. Applicants note this error in the Sequence Listing, but respectfully submit that the specification correctly identifies the amino acid sequences encoded by ORFs 13 and 14 (SEQ ID NOs: 14 and 15) as having 6893 amino acids (deduced from nucleotides 19032 – 39713 of SEQ ID NO: 1), and 8695 amino acids (deduced from nucleotides 39713 – 65800 of SEQ ID NO: 1), respectively (see specification at page 12, lines 18 – 21). This error has been corrected in the corrected Sequence Listing enclosed herewith.

The Examiner notes that SEQ ID NO: 34 is 309 amino acids long and asks whether it is perhaps a duplicate of ORF 23. Applicants note that by coincidence the amino acid sequences for ORF 23 (SEQ ID NO: 24) and ORF 33 (SEQ ID NO. 34) both have 309 amino acid residues; however, the amino acid sequences of SEQ ID NOs: 24 and 34 are different and believed to be correct in the original Sequence Listing as filed.

Applicants' representative has also noted the following additional errors in the sequence listing as originally filed. On page 4 of the sequence listing as originally filed, ORF 32 (corresponding to SEQ ID NO: 33) was erroneously indicated in the "misc_feature" entry as having positive strandedness. In the corrected sequence listing submitted herewith, ORF 32 is now correctly indicated as being encoded by the negative strand. This

correction is supported by the amino acid sequence itself, which has been correctly represented as SEQ ID NO: 33 in the sequence listing as filed, lines 15-16 of page 14 of the description, where the start and stop points for ORF 32 are indicated and it is noted that it is encoded by the antisense strand, and the start and stop points for ORF 32 indicated as (87372)...(86803) in the "misc_feature" entry of the sequence listing as filed, the order of the numbers (larger to smaller) indicating that it is encoded by the negative or antisense strand.

In addition, Applicants' representative has noticed that in SEQ ID NO: 14 (corresponding to ORF 13) in the sequence listing as originally filed, an isoleucine (Ile) residue at position 1801 was inadvertently omitted. Similarly, in SEQ ID NO: 15 (corresponding to ORF 14) in the sequence listing as originally filed, a proline (Pro) residue at position 3601 was inadvertently omitted. These errors have been corrected in the replacement sequence listing submitted herewith.

The Examiner notes that the full-length, exactly-encoding DNA sequence was provided in SEQ ID NO: 1 of the Sequence Listing as originally filed, and thus, correction of the ORFs should be attainable without adding new matter. Applicants agree that the full-length DNA sequence of SEQ ID NO: 1 as originally filed fully supports the corrections to the Sequence Listing made herein, and thus, no new matter has been added. Applicants also point to the specification at page 11, line 32 to page 13, line 17 for further support for the corrections to the Sequence Listing.

**Alignment Of Full-Length DNA Contig Sequence (SEQ ID NO: 1) With Each Of Polypeptide Sequences Of SEQ ID NOS: 2-34**

The Examiner has suggested submitting an alignment of SEQ ID NO: 1 with all the amino acid sequences to identify clear support for the corrections to the Sequence Listing in the specification as originally filed. Attached hereto as Appendix A (pages 1-260) is the alignment as requested by the Examiner.

Of the polypeptides encoded by the 33 ORFs disclosed herein (SEQ ID NOS: 2-34), eighteen of these polypeptides are encoded by the positive strand of the DNA contig sequence of SEQ ID NO: 1, and fifteen are encoded by the negative strand of the DNA contig sequence of SEQ ID NO: 1. Some of the eighteen polypeptides encoded by the positive strand are overlapping. Due to the limitation of the PatentIn software, overlapping amino acid sequences cannot be represented in the same nucleic acid/amino acid alignment. Thus, in order to show alignment of all the polypeptides encoded by the positive strand, it was necessary to present the DNA contig sequence (SEQ ID NO: 1) twice in the attached alignment.

Accordingly, "SEQ ID NO: 1" of the alignment is identical to SEQ ID NO: 1 as originally filed, and has the amino acid sequences encoded by ORFs 1, 2, 3, 7, 11, 12, 14, 15, 16, 17, 18, 23, 29, 30, 31 and 33 (SEQ ID NOS: 2, 3, 4, 8, 12, 13, 15, 16, 17, 18, 19, 4, 30, 31, 32 and 34) aligned against it, consistent with the start and stop points for each of these ORFs indicated in the sequence listing as filed (as "misc_feature" entries), which are also indicated on pages 12-14 of the application as filed. "SEQ ID NO: 2" of the

alignment is identical to SEQ ID NO: 1 as originally filed, and has the amino acid sequences encoded by ORFs 13 and 19 (SEQ ID NO: 14 and 20) aligned against it.

Due to further limitations of PatentIn software, ORFs encoded by the negative strand cannot be translated from a SEQ ID NO: entry of the positive strand. Therefore, the reverse complement of SEQ ID NO: 1 has been created and is presented in the attached alignment as "SEQ ID NO: 3". The amino acid sequences corresponding to ORFs 32, 28, 27, 26, 24, 22, 20, 10, 8, 6 and 5 (SEQ ID NOS: 33, 29, 28, 27, 25, 23, 21, 11, 9, and 6), which are encoded by the negative strand of SEQ ID NO: 1, have been aligned against "SEQ ID NO: 3" of the attached alignment consistent with the start and stop points for each of these ORFs indicated in the sequence listing as filed (as "misc_feature" entries), which are also indicated on pages 12-14 of the application as filed.

Due to the inability to present alignments of overlapping ORFs noted above, the reverse complement of SEQ ID NO: 1 has duplicated as "SEQ ID NO: 4" in the attached alignment, and ORFs 25, 21, 9 and 4 (SEQ ID NOS: 26, 22, 10 and 5) are aligned against it.

To assist the Examiner, Table 1 below indicates the start and stop points of the sequences encoded by the negative strand, showing the correspondence of these points relative to the positive strand with the same start and stop points as calculated relative to the

nucleotide positions of the reverse complement sequence in "SEQ ID NO: 3" and "SEQ ID NO: 4" in the alignment submitted herewith.

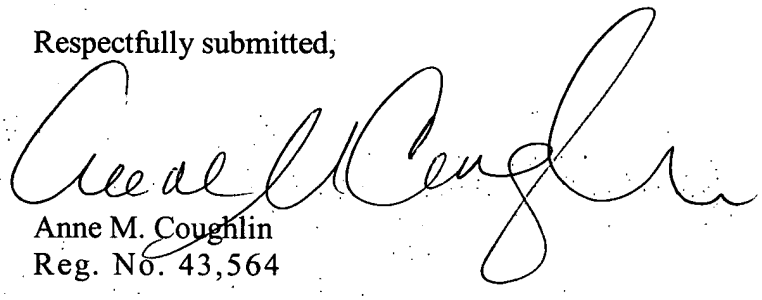
Table 1. Start and stop points of the ORFs encoded by the negative strand of SEQ ID NO: 1 as originally filed, expressed both relative to SEQ ID NO:1 as originally filed and its reverse complement presented as "SEQ ID NOS: 3 and 4" in the alignment

| Sequence | **Start and stop points relative to SEQ ID NO: 1 as originally filed (page 12-14 of specification)** | | **Calculated start and stop points relative to reverse complement of SEQ ID NO: 1 ("SEQ ID NOS: 3 and 4" of the attached alignment** | |
|---|---|---|---|---|
| | Start | Stop | Start | Stop |
| ORF 4 | 6665 | 5814 | 81757 | 82608 |
| ORF 5 | 7703 | 6693 | 80719 | 81729 |
| ORF 6 | 9464 | 8130 | 78958 | 80292 |
| ORF 8 | 12751 | 10829 | 75671 | 77593 |
| ORF 9 | 13617 | 12802 | 74805 | 75620 |
| ORF 10 | 15203 | 13614 | 73219 | 74808 |
| ORF 20 | 73439 | 71964 | 14983 | 16458 |
| ORF 21 | 74216 | 73563 | 14206 | 14859 |
| ORF 22 | 75424 | 74213 | 12998 | 14209 |
| ORF 24 | 78110 | 76449 | 10312 | 11973 |
| ORF 25 | 79864 | 78107 | 8558 | 10315 |
| ORF 26 | 81624 | 79861 | 6798 | 8561 |
| ORF 27 | 81909 | 81682 | 6513 | 6740 |
| ORF 28 | 82346 | 82062 | 6076 | 6360 |
| ORF 32 | 87372 | 86803 | 1050 | 1619 |

**Conclusion**

In response to the Restriction Requirement, Applicants respectfully request that the claims drawn to nucleic acids and related products and methods relating to SEQ ID NOS: 13, 14, 15 and 18 (ORFs 12, 13, 14 and 17) be combined and examined together in the present application. It is believed that the present claims are in condition for allowance and early notice to that effect is respectfully solicited.

Respectfully submitted,



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Dated: February 26, 2004

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